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From apathy to addiction: insights from neurology and psychiatry

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Abstract

The tendency to engage in addictive behaviors has long been tied to the actions of the dopamine system. Early theories were based on the fact that all addictive drugs and behaviors (such as gambling) increase dopamine levels in the striatum, and the evidence that dopamine signaled reward or reward prediction error. However, with a changing emphasis of addiction away from purely pharmacological models that emphasize tolerance and withdrawal, towards one of behavioral dyscontrol, is there still a place for abnormal dopamine signaling in addiction? Here we recast the dopamine theory of addiction based on the idea that tonic dopamine may index a continuous phenotype that goes from apathy to impulsivity and compulsivity. Higher tonic dopamine signaling would make individuals vulnerable to drug reinforcement and cue-induced craving. We relate this to computational models of dopamine signaling, and review clinical and neuroimaging evidence from Parkinson's Disease, schizophrenia and bipolar disorder in support of this model.

Introduction

Addiction has typically been defined as a pharmacological dependence on a specific agent with direct pharmacological actions in the central nervous system. The emphasis has been on the dopamine system, as all known addictive drugs appear to act directly on dopamine signaling. In recent years however, addiction has been re-conceptualized as a loss of control over behavior, which is the original meaning of the word (from the latin for "enslavement'). An example of this is the recent recognition in the DSM-V of pathological gambling as a "behavioral addiction" (Fauth-Bühler et al., 2017). The emphasis on self-control and its converse, compulsive reward seeking, allows us to recast addiction as one extreme of a phenotypic trait characterized by a tendency to either avoid or to engage in maladaptive behaviors. Here we propose that there exists a motivational continuum from apathy to compulsion, and that this tendency is under the control of tonic dopamine in the striatum. According to this model, low tonic dopamine and reduced phasic bursts are associated with apathy, while high tonic dopamine and normal-to-increased phasic bursts lead to compulsive engagement in reward-seeking. We briefly review theories of motivation, the neurophysiology of dopamine, and provide evidence for the model from clinical examples in neurology and psychiatry.

Psychology and Neurophysiology of Motivation

Disorders of motivational control are a major source of individual suffering and societal financial burden. Impaired control over incentive behavior underlies drug and behavioral addiction, obesity, and is a feature of mood disorders (Michaud et al., 2017; Sharma et al., 2014). At the other end, apathy is a significant source of disability in Parkinson's Disease, depression and schizophrenia (Husain and Roiser, 2018). Motivation is placed within the Positive Valence domain of the "Research Domain Criteria" transdiagnostic framework (Nusslock and Alloy, 2017). Over the years, investigators have proposed slightly different phenotypic categories and nomenclatures related to motivation that include concepts such as impulsivity, extraversion, behavioral activation, novelty-seeking and sensation-seeking (Depue and Collins, 1999). They share a common view of reward sensitivity as an underlying personality trait that has broad influence on behaviors of clinical importance.

Motivation may be separated into specific and general components (Niv et al., 2006). For example, motive states may amplify or dampen the tendency to approach or seek out specific reward-predicting cues based on current need (e.g. energy balance modulating hunger). Motivation may also refer to a general internal drive state (or even trait) that influences response vigor non-specifically. Thus, two components can be distinguished, with dissociable neural substrates: (1) a directing component that modulates the value of rewards or actions associated with them and (2) a general energizing component (Niv et al., 2006). These authors, taking inspiration from economics, refer to this latter component as "opportunity cost" (Niv et al., 2007). When average reward rate from the environment is high, it is optimum to vigorously search for rewards (expending energy, taking risks), while low average reward rates favor inactivity. They further suggest that the opportunity cost is encoded by tonic dopamine. Thus, one can view the dopamine-mediated energizing function of motivation as favoring risk-taking and energy expenditure when rewards are likely, and conversely promoting energy conservation and risk avoidance at other times. Much of the evidence in support of this view comes from animal research. Here we review evidence from the human neurological and psychiatric literature that supports a role of tonic dopamine in modulating the energizing component of motivation. Specifically, we show that engagement in rewarding behaviours, including drug addiction, appears to vary according to tonic dopamine signaling in Parkinson's Disease, schizophrenia, and bipolar disorder. We also attempt to differentiate two different mechanisms favouring addictive behavior: (1) motivational states that result from a general increase in engagement with rewards, behavioral activation, and euphoria, which resembles hypomania, and (2) negative affective states, in which previously reinforced cue-reward associations drive behavior (e.g. drug relapse during depressive episodes).

Dopamine psychopharmacology

One of the most prominent theories of dopamine function is that phasic release encodes a reward prediction error (PE) signal important for learning (Schultz, 2013). Recent extensions of this model also link dopamine to general sensory PEs, even in the absence of obvious value (Gardner et al., 2018). However, it is difficult to link PE and learning to all aspects of addictive behaviour (García-García et al., 2017). One possibility is that greater intrinsic dopamine signaling as a trait could lead to accelerated cue-reward learning and a greater likelihood of addiction. There is some support here from animal studies (Belin et al., 2008) and computational modeling (Redish, 2004a). However, there is little evidence that humans at high risk for addiction have generally faster or more efficient reinforcement learning. The prototypical trait of addiction vulnerability, impulsivity (the tendency to act rapidly without consideration of long-term consequences) is also not easily explained in terms of reinforcement learning. Another possibility is that enhanced dopamine cue reactivity, possibly resulting from sensitization, promotes a more rapid switch from flexible context-sensitive reinforced behavior to rigid, habitual stimulus-response associations that may underpin compulsive drug seeking (Everitt and Robbins, 2016).

However, these theories do not explain why dopamine D2 agonist medications cause a state of enhanced motivation to seek out rewards, as in agonist-induced pathological gambling (Dagher

and Robbins, 2009). A more likely model derives from an alternate theory of dopamine signaling that emphasizes its role in motivation (Berridge, 2012; Salamone and Correa, 2012). Here, tonic dopamine acting in the striatum promotes the willingness to expend effort (or money) to obtain rewards, possibly by modulating the expected value or opportunity cost of a reward or an action (Niv et al., 2007). Recent evidence from animal experiments suggests that dopamine may indeed encode both reward PEs and expected value through different mechanisms (Hamid et al., 2016): the former via burst firing or suppression of dopamine neurons, the latter in part via impulse-independent dopamine release from nerve terminals in the striatum (Mohebi et al., 2019). Value coding may explain the oft-observed ramping up of dopamine levels in striatum as an animal approaches an anticipated reward (Phillips et al., 2003). By reflecting expected value, dopamine could increase the effort expended to obtain rewards, thus acting as a true motivation signal. Conversely, abnormally low dopamine could enact a state of low reward expectancy, that could be akin to apathy. In the motor domain, low dopamine could similarly entail akinesia and bradykinesia, a state in which expending effort would not be anticipated to yield rewards. Grace has suggested that an excitatory signal from ventral hippocampus indirectly regulates the population activity of dopamine neurons (Fig 1C): when dopamine neurons are relatively disinhibited, they exhibit high tonic activity and high phasic response (Grace, 2016, 2010, 1991). In this state there would be enhancement of both general motivation and specific reactivity to reward-predicting cues. Moreover, dysregulation of the ventral hippocampus to basal ganglia system is expected to lead to aberrant dopamine signaling that may underpin both apathy and compulsive behavior in stress, schizophrenia and bipolar disorder (Belujon and Grace, 2015; Grace, 2016).

The organization of basal ganglia and its dopamine innervation may explain these dual roles and provide a mechanism for value signals to be transformed into motivated action. The corticostriatal system is organized into two parallel pathways (Fig. 1A). An influential model suggests that the indirect pathway, which contains dopamine D2 receptors, is involved in inhibition (No-Go), while the direct pathway with D1 innervation is involved in action selection (Frank et al., 2004; Frank and O'Reilly, 2006). Differential dopamine signals emerge at different concentrations (Fig. 1B): tonic levels are relatively low, while phasic bursts cause transient many-fold increases in synaptic dopamine (Dreyer et al., 2010). Because D2 receptors have high affinity for dopamine, they can sense low-concentration tonic dopamine levels. In addition, D2 receptors have an inhibitory effect on the indirect pathway striatal projection neurons. This means that increases in tonic dopamine will inhibit the No-Go pathway, and promote action, while reductions in tonic dopamine will lead to inhibition. This accounts for the well-known motor and motivational deficiencies due to dopamine deficit in PD and their reversal by dopamine D2 agonist drugs. Conversely, D1 receptors have low affinity for dopamine and do not sense tonic dopamine. However, when phasic bursts occur, occupancy at D1 receptors rises considerably (Fig. 1B) and action selection is enabled. The temporally limited phasic bursts can therefore bind cues and outcomes. Finally, the model accounts for No-Go learning based on the occurrence of phasic dips in dopamine levels following negative feedback (Frank and O'Reilly, 2006). Because tonic dopamine concentration is in the steepest part of the D2R occupancy curve (Fig. 1B) the indirect system is sensitive to both increases and decreases in tonic dopamine levels from baseline, allowing it to act bi-directionally to up or down-modulate action selection. Meanwhile, phasic dopamine, reflecting the PE signal, can

promote learning and selection of specific reward-producing actions. Positron Emission Tomography (PET) imaging in humans supports this dichotomy (Cox et al., 2015).

From apathy to addictive behavior: a continuous model of dopamine signaling

The term apathy describes a complex clinical syndrome prevalent in many neurological and psychiatric disorders; among these, PD, schizophrenia and bipolar disorder (Husain and Roiser, 2018; Pagonabarraga et al., 2015; Strauss and Cohen, 2017). Across these disorders, apathy is regarded as the strongest predictor of poor global functioning, diminished quality of life and general health (Faerden et al., 2013; Fervaha et al., 2015; Laatu et al., 2013; Strauss et al., 2013; Tierney et al., 2018). Apathy can be defined as impaired motivation and a quantitative reduction in goal-directed behavior (Levy and Dubois, 2006; Marin, 1996) caused by any combination of impaired self-generation of actions, effort allocation, value representation and reinforcement learning (for detailed review see (Culbreth et al., 2018; Gold et al., 2015; Hartmann-Riemer et al., 2018; Husain and Roiser, 2018; Le Heron et al., 2018; Waltz and Gold, 2016)). Diagnostic criteria for apathy have been proposed, and they consist of persistent reduction in motivation, a loss of goal-directed behaviour or cognition, and reduced emotional reactivity to positive or negative events, severe enough to cause impairment and not explainable solely by physical disability (Robert et al., 2009). Several regions within the cortico-limbic reward circuit are implicated in apathy including the ventral and dorsal striatum, anterior cingulate, orbitofrontal cortex and dorsolateral prefrontal cortex (Kos et al., 2016; Le Heron et al., 2018). Here we propose that blunted striatal dopamine function plays an important role in apathy across disorders and is inversely related to addictive behavior.

Personality traits underlie everyday behavior and are typically classified according to dimensions such as the “Big Five” (Costa and McCrae, 1992). Gray suggested that personality traits reflect the activity of motivational systems (Depue and Collins, 1999). Impulsivity is highly prevalent in several neurological and psychiatric disorders including PD, schizophrenia and bipolar disorder and has been implicated particularly in addiction (Dervaux et al., 2001; Sinha et al., 2013; Swann et al., 2004; Voon et al., 2017). A neurocognitive framework (Sharma et al., 2014) proposes three different personality axes that may underlie impulsivity: 1) Disinhibition versus Constraint/Conscientiousness (cognitive control), 2) Extraversion/Positive Emotionality/ Sensation Seeking (reward sensitivity/sensation seeking), and 3) Neuroticism/Negative Emotionality (punishment sensitivity/anxiety). The personality characteristics associated with impulsivity are low conscientiousness/high disinhibition, high neuroticism/negative emotionality and high extraversion/positive emotionality (Sharma et al. 2014). Previous work by our group has shown a personality-driven link between addiction and obesity using this model, (Michaud et al., 2017), but one can also utilize this framework to convey the relationship between apathy/anhedonia and addiction.

Here we conceptualize apathy as a reduction in spontaneously generated actions, especially relating to reward. The opposite state is characterized by vigor, compulsive engagement with rewarding stimuli, increased risk taking and impulsivity, and euphoria. Note that others have questioned whether such a simple dichotomy fits the underlying neurobiology (Sinha et al., 2013). These authors argue that dopaminergic control of motivated behavior can be divided

into neurobiologically separable components. Nonetheless, in the following, we will provide evidence for a bidirectional model of dopamine dysfunction and an apathy-addiction continuum from three different neurological and psychiatric disorders: Parkinson's Disease (PD), schizophrenia, and bipolar disorder. In each of these disorders, we will review the clinical and neuroimaging literature and address current conceptualizations of dopamine signaling.

Parkinson's Disease

PD is a multisystem neurodegenerative disorder characterized by the formation of Lewy bodies with accumulated α-synuclein and neuronal loss spreading over time (Alexander, 2004; McGregor and Nelson, 2019). The most prominent symptoms are due to loss of dopaminergic neurons connecting the substantia nigra pars compacta (SNc) with the dorsal striatum and, to a lesser extent, adjacent dopaminergic neurons connecting the ventral tegmental area (VTA) with the ventral striatum. While motor symptoms form the diagnostic hallmark of PD, apathy is amongst the most common non-motor symptoms, affecting as many as 70% of patients (Aarsland et al., 2009), and recognized as one of the greatest sources of distress (Pont-Sunyer et al., 2015). Depression and anhedonia are also frequent, but they appear to be dissociable from apathy (Kirsch-Darrow et al., 2011).

The striatal dopamine deficit in PD critically alters both the direct action selection and indirect Go / No-Go pathways providing a mechanistic framework to explain core motor symptoms (bradykinesia and akinesia), cognitive, and motivational deficits (Albin et al., 1989; Frank et al., 2004; García-García et al., 2017). In the unmedicated state, PD patients have reduced phasic and tonic dopamine signaling. Low tonic dopamine leads to an overactivation of the indirect pathway (less inhibition via D2 receptors on medium spiny neurons) and enhanced No-Go signaling resulting in difficulties to initiate movements and engage in goal-directed behavior (Frank, 2005; García-García et al., 2017). In parallel, phasic dopamine release is reduced, which suppresses the direct pathway (less activation via D1 receptors on medium spiny neurons) and impairs learning from positive reward PEs and formation of cue-reward associations (Frank, 2005; Frank et al., 2004). Computational modelling and empirical work show that the mechanisms responsible for impaired action initiation also play a role in cognitive deficits in PD (Cools et al., 2010; Frank, 2005; Moustafa et al., 2008).

Excessive indirect and reduced direct pathway signaling in the cognitive and limbic portions of the striatum are both expected to result in reduced action selection, which could be linked to reduced goal-directed behavior manifesting as apathy. Indeed, imaging studies using fluorodeoxyglucose PET (FDG-PET) (measure for general metabolic activity) and [^{11}C]raclopride PET (selective dopamine D2/D3 antagonist to assess receptor availability and striatal dopamine concentration) provide evidence for reduced striatal dopamine function in PD patients with apathy. Using FDG-PET in 44 PD patients undergoing deep brain stimulation, Robert et al showed an association between decreased striatum metabolism and apathy controlling for potential confounds such as medication (Robert et al., 2014). In a comparison of PD patients with and without apathy after deep brain stimulation surgery in a methylphenidate challenge study with [^{11}C]raclopride PET, patients with apathy showed increased baseline [^{11}C]raclopride binding in the striatum (interpretable as reduced endogenous

synaptic dopamine levels) and blunted striatal dopamine release after administration of methylphenidate (Thobois et al., 2010). These authors speculated that apathy, which occurred post-operatively in half the patients, could be attributable to a reduction in dosage of dopamine agonist medication after deep brain stimulation. The PET results suggest that individuals with the lowest tonic levels of striatal dopamine were most vulnerable to apathy following dopamine agonist withdrawal. With respect to striatal reward response (activation of the direct action selection pathway), a task-based [^{15}O]H_2O PET imaging study found reduced striatal blood flow in PD patients with high apathy during monetary choices compared to patients with low apathy (Lawrence et al., 2011). This finding supports a relationship between reduced striatal activation during reward processing and apathy. In corroboration with this, an EEG study showed reduced feedback-related negativity during a gambling task in PD patients with apathy. This signal is thought to reflect mesocortical dopamine PE signaling (Martínez-Horta et al., 2014). Taken together, computational, behavioral and imaging findings provide compelling evidence for a hypodopaminergic state underlying impaired direct and indirect pathway signaling in PD, which manifests as bradykinesia but also cognitive deficits and apathy.

PD patients tend not to suffer from substance use disorders (Dagher and Robbins, 2009). The notion of a 'parkinsonian personality' goes back to the early 20th century and remained popular in the psychoanalytical literature of the forties and fifties. Controlled studies confirmed the existence of personality traits described as rigid, introverted, and slow tempered prior to the onset of motor symptoms in PD (Todes and Lees, 1985). Recent studies and meta-analyses have refined our view on personality profiles in PD, identifying low Openness, Extraversion and novelty-seeking but high Neuroticism and Harm avoidance. Accordingly, lower rates of nicotine and alcohol consumption have been identified as risk factors for developing PD (Breckenridge et al., 2016; Noyce et al., 2012). It has been suggested that low sensation seeking (which is similar to novelty-seeking) might be the reason for lower smoking and alcohol consumption rates in PD (Evans et al., 2006a).

Because of the foregoing, clinicians in the early 2000s were surprised to see impulse control disorders and behavioral addiction emerge in 15% to 60% of PD patients after the initiation of dopaminergic therapy (Molde et al., 2018; Weintraub et al., 2010). While apathy is directly linked to the primary underlying pathophysiology of PD, impulsivity and addictive behavior occur almost only as a consequence of dopamine replacement therapy (DRT), especially when the therapy involves dopamine D2 agonists. The spectrum of observed maladaptive behavior includes pathological gambling, hypersexuality, binge eating, compulsive shopping, hoarding, and kleptomania (Molde et al., 2018; Weintraub et al., 2010). In addition, certain patients voluntarily overdose their medication and even become addicted to it (Ambermoon et al., 2012; Dagher and Robbins, 2009; Lawrence et al., 2003). Interestingly, demographic and personality risk factors for these addictive behaviors mirror those in the general population: higher novelty-seeking, personal or family history of alcohol use disorders, male and younger age (Dagher and Robbins, 2009; Voon et al., 2007). Adding to this, empirical findings showed that initiation of dopaminergic treatment increases novelty-seeking and reward sensitivity thereby potentially increasing the risk for addiction in medicated PD patients (Bódi et al., 2009).

Whether behavioral addiction or drug abuse dominate the clinical picture depends on the type of DRT. Dopamine agonists, such as pramipexole or ropinirole, are typically implicated in behavioral addiction in PD (Averbeck et al., 2014; Voon et al., 2006; Weintraub et al., 2010), while levodopa is the most frequently abused medication (Ambermoon et al., 2012). Behavioral addictions typically resolve after dopamine agonist discontinuation (Corvol et al., 2018; Mamikonyan et al., 2008; Singh et al., 2007). In sum, there is strong empirical evidence that DRT-induced 'hyperdopaminergic states' are the cause of impulse control disorders and addiction in PD (Sinha et al., 2013). It should be noted that dopamine agonists may also favor the development of addictive syndromes when administered to patients with restless leg syndrome (Voon et al., 2011b).

The fact that dopamine D2 agonists tend to favor the emergence of addictions, but are not addictive, while levodopa itself may become addictive, provides insights into the theory of an apathy-addiction continuum. The clinically approved DA agonists that cause addictions act specifically at the D2/D3 receptor family, with little D1 action (exception: apomorphine, which is a D1 and D2 agonist) (Dagher, 2012). Hence, postsynaptic tonic D2 receptor stimulation (reduction of phasic dopamine dips) of medium spiny neurons in the striatum "releases the brake" by inactivating the indirect/No-Go pathway (Frank et al., 2004) and inducing long-term depression (Kreitzer and Malenka, 2007; Shen et al., 2008). Thus, dopamine agonists exert their reinforcing and 'addictive' effects via reduced No-Go learning (learning from negative feedback) and could promote or enhance the effects of other reinforcers and already learned behaviors (e.g. hypersexuality or gambling) (Dagher, 2012). At the same time, dopamine agonists stimulate presynaptic D2 receptors in the SN/VTA and thereby reduce phasic bursts related to the rewards or conditioned cues (less activation of the direct action selection pathway via D1 receptors). This could explain why dopamine agonists have little endogenous reinforcing effect compared to other drugs of abuse or levodopa (Pierce and Kumaresan, 2006; Redish, 2004b; Volkow and Morales, 2015).

In contrast, levodopa, a dopamine precursor, simply increases available dopamine and therefore acts on both D1 and D2 dopamine receptors (Dagher, 2012). Thus, levodopa increases phasic dopamine bursts on D1 receptor medium spiny neurons of the direct pathway and enhances action selection and learning from positive PEs (positive reinforcement learning) (Garcia-Garcia et al., 2017; Pessiglione et al., 2006). Simultaneously, the levodopa effect on postsynaptic D2 receptors, which inactivates the indirect pathway, reduces No-Go signaling which could further enhance its reinforcing effects (García-García et al., 2017). While the foregoing is thought to explain why levodopa is addictive but does not promote other addictions (and indeed the clinical recommendation is to switch patients from dopamine agonists to levodopa when they develop behavioral addictions), it should be noted that in the early days of levodopa, when very high doses were administered (prior to the introduction of carbidopa), compulsive behaviors were often observed. Indeed, Oliver Sacks described cases of levodopa-induced compulsive sexuality and psychomotor agitation in the 1960s (Sacks and Kohl, 1970). Note also that repeated administration of levodopa leads to sensitization of dopamine neurons, which could then promote persistent increases in tonic dopamine signaling (Harden and Grace, 1995).

Computational, behavioral and imaging studies provide support for these clinical observations in PD. PD patients ON dopaminergic medication demonstrate impaired learning from negative outcomes and intact or increased learning from positive outcomes (Cools et al., 2006; Frank, 2005; Frank et al., 2004; Mathar et al., 2017; Rutledge et al., 2009; Skvortsova et al., 2017). Moreover, PET imaging studies show abnormal striatal dopamine signaling in PD patients with addictions or impulsive behavior (Frosini et al., 2010; Politis et al., 2013; Steeves et al., 2009; Wu et al., 2015). Enhanced striatal dopamine concentration was observed after levodopa administration in patients with levodopa dependence (Evans et al., 2006b), at rest, while gambling in patients with pathological gambling (Steeves et al., 2009), and during reward cue exposure across patients with different addictive behaviors (O'Sullivan et al., 2011; Wu et al., 2015). Additionally, levodopa-induced sensitization of striatal dopamine neurotransmission correlated with self-reported "wanting" of levodopa (Evans et al., 2006b). It should be noted however that measures of reduced [^{11}C]raclopride binding potential OFF medication (Payer et al., 2015; Stark et al., 2018; Steeves et al., 2009) could also reflect reduced postsynaptic D2/D3 receptor expression instead of increased extracellular dopamine release.

Similarly, fMRI studies have reported increased cue-related ventral striatum blood oxygen level dependent (BOLD) activation in PD patients with pathological gambling (Frosini et al., 2010) and hypersexuality (Politis et al., 2013). Correspondingly, PD patients with behavioral addictions showed enhanced ventral striatum activation in response to predicted gain (Voon et al., 2010) as well as increased risk taking and striatal activation during risky choices (Voon et al., 2011a).

Single photon emission computed tomography has been used to image striatal dopamine transporter DAT levels in PD. There are reports of reduced striatal DAT expression in PD patients with behavioral addictions (Cilia et al., 2010; Voon et al., 2014), which could lead to relatively higher tonic dopamine levels. Reduced DAT availability in striatum may also be considered a vulnerability factor as it has been shown to precede the development of addictions in PD patients (Vriend et al., 2014).

There are other studies providing evidence for cortico-striatal reward network dysfunction beyond localized striatal alterations. Politis and colleagues reported sexual-cue induced hyperactivation in PD patients with hypersexuality not only in the striatum but across regions of the salience and limbic networks including the amygdala, anterior cingulate and orbitofrontal cortex (Politis et al., 2013). Using PET imaging in a mixed sample of PD patients with different impulse control disorders (e.g., pathological gambling, hypersexuality, and compulsive eating), Joutsa and colleagues reported enhanced baseline [18F]fluorodopa uptake in the medial orbitofrontal cortex (Joutsa et al., 2012). Finally, it should be noted that other neuroimaging studies have implicated large scale brain networks that extend beyond the striatum in addiction in PD (Ruitenberg et al., 2018; Tessitore et al., 2017a, 2017b; Voon et al., 2017).

In sum, the evidence, from computational, behavioral and imaging studies in PD strongly supports the theory that low dopamine signaling is associated with apathy and reduced engagement in reward seeking, while tonic increases in mesolimbic dopamine secondary to

dopamine agonist therapy promote the development of compulsive reward seeking and addiction.

Schizophrenia

Schizophrenia is characterized by heterogeneous clinical manifestations that are often classified into positive symptoms (e.g. hallucination, delusion), negative symptoms (e.g. apathy, anhedonia, blunted affect, alogia), affective symptoms (e.g. depression, mania), and cognitive symptoms (Mueser and McGurk, 2004; van Os and Kapur, 2009). Of note, different symptoms often appear simultaneously, which makes it sometimes difficult to assign them to a specific dimension. For example, negative symptoms such as apathy and anhedonia can manifest with or without concurrent depression (Carpenter et al., 1985; Galderisi et al., 2018; Kirkpatrick, 2014; Kirschner et al., 2016a). In the first scenario apathy/anhedonia are thought to be primary manifestations of the pathophysiology of schizophrenia. In the latter, depression is a cause of secondary negative symptoms that may potentially respond to adequate treatment of depression

Patients with schizophrenia have a dramatically higher lifetime prevalence of comorbid substance use disorder than the general population (40-60% vs 10-13%) (Buckley et al., 2009; Grant et al., 2016; Hunt et al., 2018; Regier et al., 1990). A recent meta-analysis in schizophrenia estimated prevalence rates of 42% for any substance use disorder, 28% for illicit drugs, 26% for cannabis, 24% for alcohol and 7% for stimulant use (Hunt et al. 2018). Gender-specific effects are similar to those of the general population with a significantly higher risk in males. The co-occurrence of drug abuse and schizophrenia is associated with earlier age of onset, and complicates treatment of both conditions (Schmidt, Hesse, and Lykke 2011; Hunt et al. 2018). Gambling addiction is also described and often co-occurs with substance abuse (Desai and Potenza, 2009).

The clinical profile of patients with schizophrenia and comorbid substance use disorders is characterized by more severe positive symptoms, fewer negative symptoms such as apathy/anhedonia and fewer cognitive deficits compared to patients without substance use (Potvin et al., 2006; Talamo et al., 2006; Wobrock et al., 2013; Yücel et al., 2012). There is evidence that patients with negative symptoms prior to substance abuse are less motivated to start or continue taking drugs. In this regard, it has been shown that patients with primary negative symptoms (deficit syndrome) show less substance abuse than patients without primary negative symptoms (Kirkpatrick et al., 1996). This observation is supported by a longitudinal study in which patients with more severe anhedonia at baseline reduced their drug consumption after 12 weeks (Potvin et al., 2008). Importantly, personality traits associated with dopamine reward circuitry hyperfunction, such as sensation-seeking and impulsivity, are also increased in those schizophrenia patients with higher risk for substance abuse (Dervaux et al., 2010, 2001; Gut-Fayand et al., 2001; Liraud and Verdoux, 2000; Zhornitsky et al., 2012). This is consistent with the evidence in PD cited earlier.

Together, these data support the hypothesis that higher anhedonia and negative symptoms, in particular prior to the onset of substance abuse, are associated with a relative protective effect.

However, cross-sectional findings of lower negative symptoms in schizophrenia patients with substance use disorder could also be explained by an opposite causal relationship (Potvin et al., 2006). Consistent with the "self-medication hypothesis" (Awad and Voruganti, 2015; Khantzian, 1997), it is possible that substance abuse improves negative symptoms at the cost of increasing positive symptoms. Indeed, Wobrock and colleagues found trend-level lower negative symptoms after 6-months (p=0.075) in patients with schizophrenia and substance use disorder compared to those without (Wobrock et al., 2013). However, this effect was not observed when analysis was restricted only to schizophrenia patients with recent initiation of substance abuse (i.e. excluding those with lifetime diagnosis). Contrary to the self-medication hypothesis, a recent longitudinal study in 266 patients with first episode psychosis did not find long-term beneficial effects of substance abuse on negative symptoms (Weibell et al., 2017). Over a 10-year period, patients with persistent substance abuse showed a significantly greater prevalence of negative symptoms compared to those who stopped using drugs. This is in line with longitudinal data from substance-dependent populations without schizophrenia showing that anhedonia appears to be a consequence of substance abuse or dependence, increases over time, and diminishes with abstinence (Garfield et al., 2014).

Thus, based on the available literature, it is still difficult to draw a conclusion on whether severity of substance abuse is cause or consequence of clinical features. Of note, our proposed "protection" model ("primary negative symptoms reduce the risk of substance abuse") and the self-medication hypothesis ("substance abuse improves negative symptoms") are not mutually exclusive. It is possible that primary negative symptoms have a general effect of reducing the risk to take drugs in schizophrenia, while, in those individuals with schizophrenia and pre-existing comorbid substance use disorder, substance use could potentially improve negative symptoms. In the latter case, negative affective states may come to act as cues that increase drug use in a goal-directed way (Hogarth, 2020).

Although the reasons for the comorbidity between schizophrenia and substance use are still poorly understood, shared predisposing factors have been identified. Indeed, schizophrenia and addiction have several risk factors and underlying mechanisms in common. Among these are, environmental factors such as cognitive, social, educational and vocational functioning, poverty, victimization (Mueser et al., 1990), personality traits (Jylhä et al., 2011; Khan et al., 2005; Sharma et al., 2014), genetic overlap (the 23andMe Research Team et al., 2018; Vink and Schellekens, 2018; Walters et al., 2018) as well as commonality in implicated neurocircuitries and neurobiology (Hägele et al., 2014; Khokhar et al., 2018; Luijten et al., 2017; Radua et al., 2015). For example, neuroplastic adaptations within midbrain dopamine projections to the ventral and dorsal striatum promote drug seeking behavior and play a key role in the transition from recreational substance use to addiction (Kalivas and O'Brien, 2008; Koob and Volkow, 2010). Dopaminergic signaling in the ventral striatum (mesolimbic circuit) mediates acute reinforcing and rewarding effects of drugs of abuse, while the transitions to habitual and finally compulsive drug taking in addiction are thought to be mediated by a shift to signaling in the dorsal striatum (mesoassociative circuit) (Everitt et al., 2008; Everitt and Robbins, 2016). Both of these dopaminergic circuitries function abnormally in schizophrenia (Heinz and Schlagenhauf, 2010; Kirschner et al., 2018a, 2016b; Maia and Frank, 2017). Accumulating evidence from PET imaging shows that dopaminergic dysfunction in

schizophrenia is greatest within the dorsal striatum (McCutcheon et al., 2018) while numerous fMRI studies have demonstrated aberrant activation of the ventral striatum in patients with schizophrenia (Kirschner et al., 2018b; Radua et al., 2015)

As for PD, individual differences in dopamine function seen in the general population could also modulate the risk of drug abuse and addiction in schizophrenia (Dagher and Robbins, 2009; Khokhar et al., 2018; Krystal et al., 2006; Volkow, 2009). However, unlike in PD, models of dopamine dysfunction in schizophrenia are less well tied to clearly-defined localized neurodegenerative processes and a direct causal relationship to dopaminergic drug treatment. Nonetheless, neuroimaging research over the last 20 years has provided compelling evidence for aberrant elevated striatal dopamine function in schizophrenia, caused by increased presynaptic dopamine synthesis capacity and dopamine release (Fusar-Poli and Meyer-Lindenberg, 2013; Howes et al., 2012; Weinstein et al., 2017). This hyperdopaminergic state is associated with positive symptom severity (Breier et al., 1997; Laruelle et al., 1999, 1996) increased psychosocial stress (Mizrahi et al., 2012) and can already be detected in prodromal stages (Fusar-Poli et al., 2011; Soliman et al., 2008).

Computational models have attempted to relate aberrant dopamine signaling in schizophrenia to different symptom clusters. Elevated presynaptic striatal dopamine function can lead to abnormal "chaotic" spontaneous phasic bursts in response to neutral ('irrelevant') stimuli, leading to inappropriate or maladaptive reward PEs. This aberrant reinforcement learning might underpin positive symptoms, but may also favor the development of substance use disorders (Maia and Frank, 2017). Concurrently, increases in tonic dopamine inhibiting the indirect/No-Go pathway could further impair reinforcement learning by diminishing the effects of phasic dips in dopamine during negative feedback (Frank, 2005). Together, these mechanisms underpin the 'salience dysfunction hypothesis', in which chaotic spontaneous phasic bursts lead to "aberrant valuation and gating of thoughts and perceptions", leading to delusions and hallucinations (Heinz, 2002; Heinz and Schlagenhauf, 2010; Kapur, 2003; Winton-Brown et al., 2014). FMRI studies have confirmed this mechanistic explanation showing that schizophrenia patients had increased ventral striatum (Jensen et al., 2008; Murray et al., 2008) and midbrain BOLD activity (Jensen et al., 2008; Murray et al., 2008; Romaniuk et al., 2010) in response to neutral 'irrelevant' compared to relevant cues . Both aberrant ventral striatum and midbrain activity correlated with positive symptoms (Roiser et al., 2013) (Romaniuk et al., 2010).

In line with a combined model of increased phasic and tonic dopamine, other fMRI studies found evidence for a general oversensitivity of striatal dopamine function with intact reward response (Kirschner et al., 2016c; Morris et al., 2015, 2012; Wotruba et al., 2014). Critically, increased BOLD response to reward cues was associated with positive symptoms across all stages of the schizophrenia spectrum including unmedicated individuals with ultra-high risk (Wotruba et al., 2014), schizotypy, first episode psychosis (Kirschner et al., 2016c) and chronic schizophrenia (Morris et al., 2015, 2012). In addition, an elegant multimodal fMRI/PET imaging study in healthy participants demonstrated a direct link between increased aberrant salience attribution and elevated dopamine synthesis capacity (Boehme et al., 2015). Taken

together, these findings support a model of increased phasic and tonic striatal dopamine levels underpinning positive symptoms resulting from aberrant reinforcement learning.

Given that aberrant reinforcement is often thought to be the key feature of the transition from drug use to addiction, how does the foregoing model explain the increased risk for substance abuse and addictive behavior in schizophrenia? It is possible that a "high tuned" dopamine system in adolescents at risk for psychosis and individuals in pre-psychotic states renders them more susceptible to the reinforcing effects of drugs of abuse as well as to the development of sensitization (Berridge et al., 2009; Krystal et al., 2006; Peciña et al., 2003; Robinson and Berridge, 1993). Indeed, patients with schizophrenia show enhanced reward sensitivity (euphoria and stimulatory effects) in response to alcohol (D'Souza et al., 2006). Behavioral and neuroimaging studies reported increased craving ('wanting') and cue reactivity ("sensitivity to drug cues") in patients with substance use disorder and schizophrenia (Fonder et al., 2005; Freeman et al., 2014; Moran et al., 2018; Potvin et al., 2016; Smelson et al., 2002). In addition, schizophrenia patients with higher impulsivity showed elevated striatal activation during reward anticipation, suggesting a higher propensity for risk-taking and drug use (Fig. 2). Note however that other brain systems may also be involved in addiction in schizophrenia (Moran et al., 2018). In sum, there is converging evidence from pre-clinical (Berg et al., 2011; Chambers et al., 2010), clinical, behavioral and neuroimaging studies that elevated striatal dopamine signaling promotes impulsive and addictive behavior in schizophrenia.

On the other hand, and in line with our continuum model, we propose that patients with greater apathy and negative symptoms are less likely to begin to abuse drugs. This is supported by numerous fMRI studies showing that blunted striatal activation during reward processing is associated with apathy and anhedonia in schizophrenia (Dowd et al., 2016; Dowd and Barch, 2012; Kirschner et al., 2015; Moran et al., 2019; Morris et al., 2015; Mucci et al., 2015; Simon et al., 2010; Stepien et al., 2018; Waltz et al., 2018, 2008; Wolf et al., 2014) (see also Fig.2). It is difficult to make a direct inference between fMRI BOLD and dopamine signaling; however, animal and human studies support a relationship between the two (Ferenczi et al., 2016; Garcia-Garcia et al., 2017).

Nonetheless, negative symptoms and elevated striatal dopamine transmission are both described in schizophrenia, and may co-occur. Maia and Frank's previously cited computational framework also provides a possible explanation for this paradox (Maia and Frank, 2017). Elevated striatal dopamine synthesis capacity in schizophrenia is expected to increase both tonic dopamine and spontaneous phasic dopamine release, but simultaneously cause reductions in cue-induced phasic dopamine release in response to relevant stimuli due to D2 autoreceptor stimulation (from elevated tonic dopamine). The latter may be responsible for the development of negative symptoms, in particular apathy/anhedonia. More specifically reduced phasic dopamine firing in response to "relevant" stimuli, such as reward cues, causes a) reduced reward learning (reduced PE of outcome) and b) hypoactivation during reward anticipation (reduced PE of reward predicting cue). This in turn causes reduced value/reward learning and impairs action-outcome selection, which ultimately leads to motivational deficits and a reduction in goal directed behavior (Maia and Frank, 2017; Schlagenhauf et al., 2014). Such a striatal hyperdopaminergic state with co-occurrence of increased spontaneous and

decreased reward-related phasic dopamine firing has been demonstrated in animal models of amphetamine use (Daberkow et al., 2013). Additionally, psychotogenic methamphetamine doses impair reward learning and reduce ventral striatum PE signaling in healthy participants (Bernacer et al., 2013).

This model provides an explanation for coexisting positive (spontaneous phasic bursts) and negative symptoms (reduced phasic bursts in response to reward). It is more difficult to apply to episodes with predominantly negative symptoms in the absence of positive symptoms. To account for this, it is possible that aberrant striatal dopamine function in schizophrenia is subject to dynamic fluctuations with episodes of lower tonic dopamine levels. Transient lower tonic dopamine would provoke a general inhibition of striatal signalling similar to unmedicated PD, with blunted striatal activation and negative symptoms. Additionally, apathy may also occur as a side-effect of antipsychotic medications (Kirschner et al., 2016a) or as a result of prefrontal hypofunction in schizophrenia (Fusar-Poli et al., 2011).

Of note, the hypothesized mechanisms of apathy in schizophrenia would reduce striatal gating of cue-reward associations and thereby diminish the sensitivity to drugs and drug-related cues. It should be noted again that these considerations apply to patients with apathy prior to chronic drug exposure and provide a mechanism to explain why primary apathy is not a driving force to promote addictive behavior. In contrast to this, chronic substance abuse is an underlying source for secondary apathy and anhedonia in patients with and without schizophrenia (Garfield et al., 2014; Kirschner et al., 2016a) potentially due to downregulation of the dopamine system (Ashok et al., 2017b). The latter is in line with the construct of negative reinforcement during the withdrawal/negative emotional state in chronic addiction, which is driven by reduced dopamine reward function and recruitment of brain stress systems (Koob and Schulkin, 2019; Koob and Volkow, 2010). In simplified terms, the evidence is that apathy does not cause addiction, but addiction may cause apathy and anhedonia, further promoting drug use.

Bipolar Disorder

Bipolar disorder is characterized by fluctuations in mood state and energy on a continuum between depression, hypomania, and mania (Grande et al., 2016). Similar to schizophrenia, substance abuse and addiction occur frequently in patients with bipolar disorders, with lifetime prevalence ranging from 20 to 55% (Hunt et al., 2016). A recent meta-analysis estimated prevalence rates around 25 to 30% for alcohol, 8 to 21% for cannabis, 7 to 12% for cocaine, 5 to 7% for amphetamines and around 5% for opiates (Hunt et al., 2016). Problem gambling is also three to four times higher in patients with bipolar disorder than the general population (Jones et al., 2015). Manic episodes are especially associated with substance abuse and are a risk factor for substance use disorder and problem gambling, along with male sex and a history of suicidality (Jones et al., 2015; Messer et al., 2017). Greater severity of manic episodes is associated with an increased likelihood of substance use disorder (Goldstein et al., 2013), and patients with current substance use disorder tend to have had more severe manic phases (Teter et al., 2011). Impulsive behavior is a key component of mania and is increased additively when bipolar disorder and substance abuse coexist, suggesting a link between impulsivity and substance abuse in these individuals (Moeller et al., 2001; Swann et al., 2004). The foregoing

supports a model wherein manic episodes, associated with elevated dopamine signaling, promote both concurrent and lifelong drug use or behavioral addiction. However, it should be noted that not all studies show a temporal link between mood states and substance use (Zaane et al., 2014). Apathy is also seen in bipolar disorder, with severity similar to schizophrenia, which can persist even in euthymic phases and become chronic (Kirschner et al., 2019; Strauss and Cohen, 2017). One would predict reduced addictive behavior linked to apathy however, to our knowledge, data do not currently exist to test this theory.

In line with these empirical findings, fMRI studies have shown cortico-striatal reward system dysfunction in bipolar disorder (Caseras et al., 2013; Kirschner et al., 2019; Redlich et al., 2015; Yip et al., 2015) and provided evidence for a transdiagnostic mechanism across substance use disorders, mood disorders and schizophrenia (Hägele et al., 2014). Nevertheless, an integrative dopamine model is less established in bipolar disorder than in schizophrenia or PD, partly due to the challenge in stratifying patients from specific mood states and a general paucity of PET imaging studies (Ashok et al., 2017a). Based on the existing literature Ashok and colleagues proposed a model of increased dopaminergic neurotransmission via elevation in striatal D2/3 receptor availability causing mania. Correspondingly, increased striatal DAT expression (hypothetically as a compensatory mechanism in response to higher dopamine turnover) leads to reduced dopaminergic function and periods of depression (Ashok et al., 2017a). An elegant transdiagnostic [^{18}F]-DOPA PET imaging study including patients with bipolar disorder and schizophrenia extended this model showing increased dopamine synthesis capacity (compared to controls) in bipolar disorder, to a degree comparable to schizophrenia (Jauhar et al., 2017). In line with previous studies in schizophrenia, positive symptoms were associated with increased dopamine synthesis capacity irrespective of diagnosis (Jauhar et al., 2017). Although some of the receptor and transporter alterations clearly differ between bipolar disorder, schizophrenia and PD, the effects of phasic and tonic dopamine could show a similar pattern with respect to addiction. One would predict that elevated dopamine signaling in mania should cause increased impulsive behavior and motor drive, to ultimately promote addictive behavior.

Limitations and Concluding Remarks

We provide evidence from clinical medicine that the propensity to engage in addictive behaviors is in part a consequence of tonic dopamine signaling, which indexes a phenotypic spectrum from apathy to addiction. However, there are limitations to this model. First, we focussed on dopamine signaling in the striatum as a value and motivational signal that either promotes of inhibits reward seeking. However, there are other brain systems and psychological traits associated with addiction. For example, self-regulation is related to frontal lobe function and to the personality dimension of Conscientiousness (Sharma et al., 2014). This trait may be distinct from the apathy-addiction continuum proposed here.

Second, the evidence cited for a tonic dopamine continuum from apathy to addiction is well established in PD, somewhat less so in schizophrenia, and mostly speculative in bipolar disorder (due to more limited evidence). Transdiagnostic research in addiction comorbidity with neurological and psychiatric illness would help test our model.

Also, it is important to distinguish apathy from other types of negative affect. A prominent theory of addiction views anhedonia as a persistent motivating factor for compulsive drug use (Koob and Schulkin, 2019; Koob and Volkow, 2010). Hedonic dysregulation and stress reactivity, and the personality trait of Neuroticism, are clearly associated with acute and long-term use of addictive substances (Michaud et al., 2017; Terracciano et al., 2008). Indeed, episodes of depression and negative affect (including anxiety and anhedonia) are often associated with increased drug use and relapse among drug addicts (Balsamo et al., 2016; Mathew et al., 2017; Prisciandaro et al., 2012). This may appear to contradict the model proposed here; however, our proposal only attempts to relate apathy and reduced drug use. Even though apathy and anhedonia often co-occur across a range of diagnostic categories, they likely map onto different neural and neurotransmitter systems (Berridge et al., 2009). For example, factor analysis of questionnaire measures supports separate underlying mechanisms for apathy and anhedonia in PD (Kirsch-Darrow et al., 2011). Also, another potential mechanism for greater drug use following depressive episodes is reduced motivation to seek treatment or abstain from drug use (Balsamo et al., 2016). Here apathy could favor persistent drug use by interfering with treatment. Furthermore, there is evidence that, in drug users who have experienced episodes of depression, negative mood acts to increase the incentive value of the drug. According to this theory, negative affect would act as a discriminative stimulus that signals increased value of drug use (Mathew et al., 2017).

In sum, the clinical evidence reviewed here and the work on basal ganglia computational modeling suggest that tonic dopamine signaling contributes to the propensity to addiction. Tonic dopamine appears to encode a continuous trait from apathy to compulsive motivation. It may do this by multiplying value signals that drive behavior. Future work should aim to further delineate the neurocognitive and genetic bases of this trait.

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Figure Legend

Figure 1 – Tonic and Phasic Dopamine Signaling. A: model of the basal ganglia. Dopamine modulates learning and action selection via two segregated pathways in the cortico-striato-thalamocortical circuit: The direct (action selection) pathway and the indirect (Go / No Go) pathway. Striatal medium spiny neurons of the direct pathway express low affinity D1 receptors and project to the internal segment of the globus pallidus (Gpi) and the substantia nigra pars reticulata (SNr), which in turn disinhibits the thalamus, thereby facilitating thalamic projection to the cortex for action selection. Striatal neurons in the indirect pathway express high affinity D2 receptors and project to the external segment of the globus pallidus (GPe), by which they

reduce the tonic inhibition of the GPe on the GPi/SNr, which in turn leads to suppression of the thalamic output to the cortex. Indirect pathway neurons are organized to create center-surround inhibition of direct pathway cortico-striatal loops. Direct pathway neurons can select specific actions depending on context. Excitatory (inhibitory) projections in green (red). B: The affinity of D1 and D2 receptors explains how tonic signaling affects the indirect (D2) pathway while phasic bursts affect both the indirect and direct (D1) pathways. At tonic dopamine levels, the system is in the maximally sensitive portion of the occupancy curve for D2 receptors. In this state, increases in dopamine cause overall disinhibition of corticostriatal loops, while reductions lead to greater inhibition. Thus tonic dopamine acts a bidirectional modulator that encodes the balance between action selection and inhibition. Phasic dopamine acts on the D1R system in a unidirectional fashion. C: The population activity of VTA dopamine neurons is controlled by outputs from the ventral subiculum of the hippocampus, via the nucleus accumbens (NAC) and ventral pallidum (VP). Population activity influences tonic dopamine levels in the striatum. Taken with permission from (Grace et al., 2007) . SNc: substantia nigra pars compacta. VTA: ventral tegmental area. Data on dopamine occupancy taken from Dreyer et al (2010).

Figure 2 – Ventral Striatum Activation, Apathy and Impulsivity. Spearman rank correlations between striatal activation during reward anticipation and symptom scores. Blunted ventral striatal activation during reward anticipation is associated with severity of apathy (BNSS Apathy Factor) (r_s=-.59, p=0.016). In contrast, in the same sample there was a relationship between severity of impulsivity (BIS Total Score) and striatal activation during reward anticipation (r_s=.68, p=0.006). Data (n=16 schizophrenia patients) are obtained from Stepien et al. (2018). Correlation with BIS Score are not included in previous publication. BNSS, Brief Negative Symptoms Scale: BIS, Barratt Impulsiveness Scale

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